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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/247,054	02/09/99	ANTONIOU	M CACO-0045

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WOODCOCK WASHBURN KURTZ
MACKIEWICZ AND NORRIS
ONE LIBERTY PLACE
46TH FLOOR
PHILADEL;PHIA PA 19103

EXAMINER	
BAKER, A	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 09/26/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trad marks

Office Action Summary	Application No.	Applicant(s)	
	09/247,054	ANTONIOU ET AL.	
	Examiner	Art Unit	
	Anne-Marie Baker	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 April 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21,23 and 25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-21,23 and 25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *09 February 1999* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *18* .
4) ☒ Interview Summary (PTO-413) Paper No(s). *24* .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

File

DETAILED ACTION

The after final amendment filed April 6, 2001 (Paper No. 18) has been entered. Claims 5 and 16 have been amended.

Claims 1-21, 23, and 25 are pending in the instant application.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-21, 23, and 25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-21, 23, and 25 are indefinite in their recitation of "episomal" because the definition offered in the specification is different from that known in the art. At page 5, in the last paragraph, the specification states that "[t]he term episomal vector refers to a nucleic acid vector which may be linear or circular, and which is usually double stranded in form." However, this definition is very broad and does not include the requirement that the vector be capable of integrating into the chromosome. The art teaches that plasmids are small genetic elements that replicate autonomously in the cytoplasm of a prokaryotic or eukaryotic cell (see p. 696, Elseth et al., 1995). The art further teaches that an episome is a genetic element that can replicate autonomously in the cytoplasm of the host cell or can be inserted into the chromosome of the host cell (see p. 689, Elseth et al., 1995). Thus, plasmids with this dual replicative ability are known as episomes. Some, but not all plasmids can integrate into the chromosome, such plasmids being designated episomes. Episomes,

such as the F factor, contain integration sequences that allow them to integrate into the chromosome (pp. 188-189, Elseth et al., 1995). Given the definition of "episomal" as set forth in the specification, the claims read on plasmid vectors that do not integrate into the chromosome. The specification appears to use the term "episomal" as a synonym for "plasmid."

Claims 1 and 6-11 are indefinite in their recitation of "for expressing a gene of interest in a host cell" because the structural elements recited in the claims do not include a gene of interest. Thus, it is unclear how the vector could be used to express a gene of interest in the absence of a gene of interest. Furthermore, Claim 11 is indefinite in its recitation of "a eukaryotic transcription termination sequence placed between the LCR and the gene of interest" because the vector does not already comprise a gene of interest. Thus, in Claim 11, the phrase "the gene of interest" lacks antecedent basis. It is suggested that Claim 11 be amended to depend from Claim 2 which recites that the vector further comprises "a gene of interest operatively linked to the LCR, or component thereof."

Claims 3 and 5 are indefinite in their recitation of "the component of an LCR" because the phrase lacks antecedent basis.

Claims 3 and 5 are indefinite in their recitation of "wherein the component of an LCR is a component of the β-globin LCR..." because it is unclear if Claims 3 and 5 are intended to be limited to the specific components recited therein or not. Claim 2, from which Claims 3 and 5 depend, recites that the gene of interest is operatively linked to "the LCR, or component thereof" and claims 3 and 5 recite specific components without limiting the claimed vectors to these specifically recited components. Claims 3 and 5 still allow for the vector to comprise the entire LCR rather than just the specifically recited components.

Claim 14 is indefinite in its recitation of "wherein the component of an LCR is a component of the β-globin LCR HS3" because it is unclear what component of HS3 is being referred to. In the amendment filed

December 13, 1999 (Paper No. 7), the claims were amended to remove the phrase "consisting essentially of" but the claim amendment leaves it unclear what component is specifically referred to in the claim. Applicants are reminded that the amendment filed July 17, 2000 was not entered. Thus, the claim currently reads "[t]he pair of vectors of claim 12 wherein the component of an LCR is a component of the β-globin LCR HS3."

Claim 15 is indefinite in its recitation of "wherein the LCR, or component thereof is the β-globin LCR or component thereof excluding site HS2" because it is unclear if the limitation "excluding site HS2" applies only to the "component thereof" or also to the "β-globin LCR." Thus, it is unclear if the claim still encompasses vectors comprising the entire β-globin LCR. Furthermore, if the claim intends to exclude site HS2, it is confusing for the claim to continue to recite the entire β-globin LCR because once the HS2 site is excluded, the claim is necessarily exclusively directed to a "component thereof", and no longer encompasses the embodiment wherein the entire β-globin LCR is used.

Claim 23 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01. The omitted elements are: a gene of interest. The claim is directed to a method of obtaining persistent, tissue-specific expression of a gene of interest in a host cell in culture, comprising culturing a host cell transfected with the vector of claim 1 or the pair of vectors of claim 12. However, neither the vector of Claim 1 nor the pair of vectors of Claim 12 comprise a gene of interest. Thus, it is unclear how expression of a gene of interest could be obtained in the absence of the necessary structural element, i.e. the gene of interest.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 1 and 2 are rejected under 35 U.S.C. 102(b) as being anticipated by Safaya et al. (1994).

The claims are directed to a vector having a self-replicating origin of replication and an LCR or component thereof. The vector may further comprise a gene of interest operably linked to the LCR or component thereof.

Safaya et al. disclose a plasmid vector having the HS2 site of the human β-globin locus control region (LCR). The HS2 site was situated 5' to the γ-globin gene promoter which was operably linked to the firefly luciferase gene (p. 3930, column 1, paragraph 5). The vector was used in transient expression studies. Addition of the LCR to the plasmid construct further increased γ-promoter activity.

The composition disclosed by Safaya et al. has all the structural elements recited in the claims. When the structure recited in the reference is substantially identical to that of the claims, claimed properties or functions are presumed to be inherent. See M.P.E.P. 2112.01. Thus, in the instant case, the function of the LCR component is considered an inherent property of the element and the presence of the LCR component on the plasmid can be expected to direct tissue-specific expression of the linked gene.

Thus, the claimed composition is disclosed in the prior art.

It is noted that the specification states on page 46 that "the presence of HS2 in an episomal vector results in expression of the gene of interest but not in a tissue-specific manner". The specification goes on to state "[t]herefore, a classical enhancer, such as HS2 (localized to a NF-E2/AP-1 dimer binding site within its core).....is distinguishable from an LCR or LCR component specifying tissue-specificity by the inability of the former to confer tissue specific transcription according to the invention." However, in the Declaration of Dr. Robert Crombie, filed April 6, 2001, Applicants have completely reversed their position regarding the function of the HS2 site. The Declarant states in paragraph 12 that "while Figure 5 of the application as filed may suggest that expression using HS2 alone or HS2, HS3, and HS4 may not be tissue specific, follow-up experiments confirm that they are." This further supports the argument that the presence of the LCR component on the plasmid of Safaya et al. can be expected to direct tissue-specific expression of the linked gene.

It is further noted that the preamble phrase "for expressing a gene of interest in a host cell of a specific tissue type" recites an intended use only and does not impart a structural limitation to the claimed composition. However, given that the plasmid of Safaya et al. has all the structural elements recited in the claims, the plasmid would be expected to direct tissue-specific expression of the linked gene.

It is further noted that part (b) of Claim 1 recites a property of the LCR "which when operatively linked to a gene of interest and present in a host cell directs expression of said gene in a tissue-restricted manner." In the interview of July 13, 2001, Applicants argued that this phrase is reciting a property that the LCR has in the context of the episomal vector and Applicants then further argued that the plasmid disclosed by Safaya et al. does not have this property because they only used the HS2 site. However, the Examiner must interpret the claim as broadly as reasonable. The phrase "which when operatively linked to a gene of interest and present in a host cell directs expression of said gene in a tissue-restricted manner" recites a

property of the LCR or component thereof only, and does not apply to the episomal DNA expression vector as a whole. The LCR has this property of directing tissue-specific expression of a linked gene **in its native state**, when present in a chromosome. Nothing more is required by this limitation of the claim. If Applicants' intention is to indicate that the entire vector itself has the property of conferring tissue-specific expression when it is present in a host cell, clarifying claim language is required. Given the present claim language, the Examiner interprets the limitation of part (b) as applying only to the LCR or component thereof, and not to the vector as a whole.

In the interview of July 13, 2001, Applicants argued that the plasmids of Safaya et al. are "non-replicating plasmids." However, this does not make sense, as all plasmids have an origin of replication, and plasmids are, by definition, autonomously replicating genetic elements. See the definition of Elseth et al. (1995) on page 696 which defines plasmids as small genetic elements that replicate autonomously in the cytoplasm of a prokaryotic or eukaryotic cell. On July 27, 2001, Applicants submitted several references relating to origins of replication. Applicants submitted the ATCC descriptions of the plasmids pXP2 and pT109luc. pXP2 is the parent plasmid used by Safaya et al. to make their plasmid construct comprising the HS2. Both plasmids contain the pMB1 origin of replication. In the communication of July 27, 2001, Applicants state that vectors with the pMB1 *ori* region replicate in *E. coli* and a few of its close relatives (citing Snyder et al.). While the Examiner acknowledges that this is indeed the case, it is unclear what argument Applicants are trying to make, as nothing more is required by the claims other than that the vector comprise a "self-replicating origin of replication." It is unclear what distinction Applicants are trying to make. The specification does not define a "self-replicating origin of replication", nor does it limit the "self-replicating origin of replication" to any particular type of origin of replication. Thus, any origin of replication is necessarily a "self-replicating origin of replication." Moreover, origins of replication that function in

bacteria, meet the claim limitations. Although the specification discusses using viral origins of replication as well as "mammalian sequences" (p. 13, lines 8-10), the claims are not limited to any particular type of origin of replication. On page 13, lines 14-16, the specification states that "[i]t will be understood by one of skill in the art that the invention is not limited to any one origin of replication..." Thus, it is clear that the language of the specification is not intended to limit the type of origin of replication in any way.

Claims 1, 2, and 10 are rejected under 35 U.S.C. 102(e) as being anticipated by U.S. Patent No. 6,022,738 (Atweh et al., 2000, filed March 3, 1995).

The claims are directed to a vector having a self-replicating origin of replication and an LCR or component thereof. The vector may further comprise a gene of interest operably linked to the LCR or component thereof. The vector may further comprise an antibiotic resistance gene (Claim 10).

Atweh (2000) disclose and claim vectors comprising the α-globin locus control region (α-LCR). At Column 2, lines 46-52, the disclosure reveals that the α-LCR is located 40 kb upstream of the α-globin gene cluster and its function is erythroid-specific. The disclosure further reveals that the invention is based on the discovery that vectors comprising α-LCR exhibit substantially greater stability, and consequently provide superior means for achieving erythroid-specific expression of a gene of interest (Column 2, lines 62-66). The vectors can include viral and plasmid vectors (Column 4, lines 1-2). See also Claim 1. The vectors can also include a selectable marker gene for identification of cells into which the vector has been introduced (Column 5, lines 19-25). The neomycin resistance gene is specifically contemplated (Column 5, line 23).

The composition disclosed by Atweh has all the structural elements recited in the claims. When the structure recited in the reference is substantially identical to that of the claims, claimed properties or functions

are presumed to be inherent. See MPEP 2112.01. Thus, the function of the LCR component is considered an inherent property of the element.

Thus, the claimed composition is disclosed in the prior art.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 6, 8, 9, 11, 12, 13, 17, and 19-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 6,022,738 (Atweh, 2000, filed March 3, 1995) and U.S. Patent No. 5,674,703 (Woo et al., 1997, filed December 2, 1992).

The claims are directed to a self-replicating episomal DNA expression vector comprising a self-replicating origin of replication and a locus control region.

Atweh (2000) disclose and claim vectors comprising the α-globin locus control region (α-LCR). At Column 2, lines 46-52, the disclosure reveals that the α-LCR is located 40 kb upstream of the α-globin gene cluster and its function is erythroid-specific. The disclosure further reveals that the invention is based on the discovery that vectors comprising α-LCR exhibit substantially greater stability, and consequently provide superior means for achieving erythroid-specific expression of a gene of interest (Column 2, lines 62-66). The vectors can include viral and plasmid vectors (Column 4, lines 1-2). See also Claim 1. The vectors can also include a selectable marker gene for identification of cells into which the vector has been introduced (Column 5, lines 19-25). The neomycin resistance gene is specifically contemplated (Column 5, line 23).

Woo et al. (1997) disclose and claim episomal vectors having viral origins of replication. Further, Woo et al. disclose using the episomal vectors for tissue-specific expression (Column 5, lines 35-40). Woo et al. also discloses using a pair of episomal vectors, one with a gene of interest and one encoding replication proteins (Column 6, lines 43-50). This section specifically describes a pair of episomal vectors wherein a papilloma virus origin of replication and a first promoter transcriptionally linked to a therapeutic nucleic acid sequence are contained on a first episomal vector, and a papilloma virus origin of replication, a second promoter transcriptionally linked to a papilloma virus E1 gene sequence and a third promoter transcriptionally linked to a papilloma virus E2 gene sequence are contained on a second episomal vector (Column 6, lines 43-50).

Since it would have been desirable to achieve stable expression of a gene of interest, such as one of the globin genes as discussed by Atweh, in cells in culture and *in vivo*, one of skill in the art would have been motivated to use plasmid vectors comprising an LCR as suggested by Atweh (Column 4, lines 1-2). The skilled artisan would have wanted such gene transfer vectors for use in mammalian cells. Vectors having viral origins of replication were well-known in the art as evidenced by Woo et al. Such vectors will replicate in mammalian cells. Thus, one of skill in the art would have been motivated to make plasmid vectors comprising an LCR and a viral origin of replication. Given that Atweh suggested using plasmid vectors comprising an LCR, one of skill in the art would have immediately recognized that to use such plasmids in mammalian cells would require an origin of replication that functioned in mammalian cells. Thus, it would have been apparent to the skilled artisan to use a viral origin of replication on the vectors so that they could be used in mammalian cells. Given that gene transfer into mammalian cells is an area of intense interest in the field of gene therapy, the skilled artisan would have been highly motivated to make such vectors for use in mammalian cells, particularly given Atweh's disclosure that vectors comprising α-LCR exhibit substantially

greater stability, and consequently provide superior means for achieving erythroid-specific expression of a gene of interest (Column 2, lines 62-66). Further, given that Claim 1 of U.S. Patent No. 6,022,738 encompasses plasmid vectors, the skilled artisan would have immediately recognized that the plasmid vectors of greatest value would be those that can be used in mammalian cells. Given that vectors having viral origins of replication were well-known in the art as evidenced by Woo et al., the skilled artisan would have been motivated to use a viral origin of replication on the plasmid vectors suggested by Atweh, to allow for use in gene transfer to mammalian cells. Furthermore, as disclosed by Woo et al., it would have been desirable to put the replication factors on a separate episome so that larger DNA sequences could be inserted into the episomal vector carrying the gene of interest, because the sequences encoding the replication factors (e.g., E1 and E2 of papilloma virus) would be supplied by a separate episomal vector. Therefore, it would have been obvious to one of skill in the art at the time of the invention to have included known LCR sequences in vectors having a viral origin of replication in order to achieve stable gene transfer and to have placed the gene of interest and the replication factor genes on separate episomes to allow for the use of large gene sequences.

One would have been motivated to have combined the teachings of Atweh (2000) and Woo et al. (1997) in order to make gene transfer vectors having substantially greater stability for use in gene transfer to mammalian cells.

Therefore, the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention.

Claims 7, 9, 18, and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 6,022,738 (Atweh, 2000, filed March 3, 1995) and U.S. Patent No. 5,674,703 (Woo et al., 1997, filed

December 2, 1992), as applied to claims 6, 8, 9, 11, 12, 13, 17, and 19-21 above, and further in view of Yates et al. (1985).

The claims are directed to a self-replicating episomal DNA expression vector comprising a self-replicating origin of replication and a locus control region. Each of Claims 7, 9, 18, and 19 specifically recite the Epstein-Barr virus origin of replication.

Yates et al. (1985) describe plasmids derived from Epstein-Barr virus that replicate stably in mammalian cells and are maintained as plasmids in most transformed cells. The origin of replication *oriP* was identified as the genetic element necessary for the plasmid to self-replicate and the *trans*-acting gene EBNA-1 was shown to be necessary for *oriP* function. Circular DNAs containing *oriP*, the EBNA-1 gene, and a selectable marker were found to replicate autonomously in cultured cells. Yates et al. do not teach the use of a locus control region in the EBV-based vector.

Since it would have been obvious to make plasmid vectors comprising an LCR and a viral origin of replication for the reasons discussed above (in the immediately preceding rejection), it would have also been obvious that any viral origin of replication could have been optionally used. Thus, one of skill in the art would have been motivated to use the EBV origin of replication in place of the papillomavirus origin of replication as described by Woo et al., given that the EBV origin of replication was already known in the art at the time of the instant invention. Furthermore, it would have been obvious to use the EBNA-1 gene sequence in place of the papillomavirus replication factor gene sequences, given that Yates et al. disclosed that it was necessary for replication in cultured cells.

One would have been motivated to have combined the teachings of Atweh (2000), Woo et al. (1997), and Yates et al. (1985) in order to make gene transfer vectors having substantially greater stability for use in gene transfer to mammalian cells.

Therefore, the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention.

Claim 23 is rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 6,022,738 (Atweh, 2000, filed March 3, 1995) and U.S. Patent No. 5,674,703 (Woo et al., 1997, filed December 2, 1992), as applied to claims 6, 8, 9, 11, 12, 13, 17, and 19-21 above, and further in view of Chapman et al. (1991).

Chapman et al. (1991) disclose the transfection of cultured mammalian cells with several expression vectors encoding a variety of proteins. It is common practice to transfect cultured host cells for the *in vitro* expression of a protein of interest.

Since the vectors of claim 1 are disclosed in the prior art and the vectors of claim 12 are obvious for the reasons discussed above (in the first rejection set forth under 35 U.S.C. 103(a)), these vectors could have then been used to obtain tissue-specific expression of a gene of interest in a host cell in culture. Atweh explicitly stated that the vectors comprising α-LCR exhibit substantially greater stability, and provide a superior means for achieving erythroid-specific expression of a gene of interest (Column 2, lines 62-66). As disclosed by Chapman et al., it is common practice to express a protein of interest in cultured host cells. One would have anticipated a reasonable expectation of success because the function of the genetic elements required to construct the claimed vectors are well-known in the art as evidenced by the cited references, and only standard molecular biology techniques are required to construct the claimed vectors, and only standard culturing techniques are required to express a gene of interest in a host cell in culture. Therefore, it would have been obvious to one of skill in the art at the time of the invention to have made recombinant constructs of the type claimed and to have used them to express a gene of interest in a host cell in culture.

One would have been motivated to have combined the teachings of Atweh, Woo et al., and Chapman et al. in order to have generated self-replicating, tissue-specific episomal expression vectors and to use the vectors to express a gene of interest in a host cell in culture.

Therefore, the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention.

Claim 25 is rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 6,022,738 (Atweh, 2000, filed March 3, 1995), as applied to claims 1, 2, and 10 above, and further in view of Chapman et al. (1991).

Chapman et al. (1991) disclose the effect of intron A from human cytomegalovirus immediate early gene on heterologous expression in mammalian cells.

Since it is common practice to assess the function of genetic regulatory elements in transfected cell lines, wherein the regulatory element is operably linked to a marker gene, as disclosed by Chapman et al., one skilled in the art would have been motivated to construct an episomal expression vector of the type claimed in Claims 1, 2, and 10 using candidate LCR sequences to assess the capability of the genetic element to direct tissue-restricted expression of a linked gene. One would have anticipated a reasonable expectation of success because assessing the function of genetic regulatory elements in cultured cell lines is routine experimentation and only standard molecular biology techniques and standard culture techniques are required to perform the requisite assays. Therefore, it would have been obvious to one of skill in the art at the time of the invention to have made recombinant constructs of the type claimed using candidate LCR sequences linked to a marker gene to assess the capacity of the LCR sequence to direct tissue-restricted expression of the marker gene.

One would have been motivated to have combined the teachings of Atweh (2000) and Chapman et al. (1991) in order to develop test constructs that could be assayed for function in cultured host cells.

Therefore, the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention.

Conclusion

No claim is allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne-Marie Baker whose telephone number is (703) 306-9155. The examiner can normally be reached Monday through Thursday and alternate Fridays from 9:30 AM to 7:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Karen Hauda, can be reached on (703) 305-6608. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-8724.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the patent analyst, Kay Pinkney, whose telephone number is (703) 305-3553.

Anne-Marie Baker, Ph.D.

Anne-marie Baker

ANNE-MARIE BAKER
PATENT EXAMINER